Brightline-2: MDM2–p53 antagonist BI 907828 in patients with advanced, *MDM2*-amplified, *TP53* wild-type BTC, PDAC or other selected solid tumours

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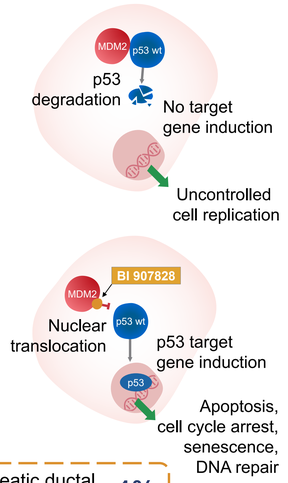
Introduction

Mechanism of action of BI 907828, an MDM2–p53 antagonist

- Inactivation of p53 is a key mechanism by which tumours promote survival and proliferation[1]
- MDM2, an E3 ubiquitin ligase, is an endogenous negative regulator of p53.[1] Blocking the MDM2–p53 interaction in *TP53* wild-type tumours represents a potential therapeutic strategy
- BI 907828 blocks the interaction between p53 and its negative regulator MDM2. This stabilises p53, permitting p53 target gene induction, leading to cell cycle arrest or apoptosis in *TP53* wild-type tumour cells[2]



MDM2 amplification prevalence

- *MDM2* is amplified in a range of tumour types, including biliary tract carcinoma and pancreatic ductal adenocarcinoma[3–5]

Biliary tract carcinoma[3,4] **5–8%**

Pancreatic ductal adenocarcinoma[5] **1%**

Bladder cancer[5] **8%**

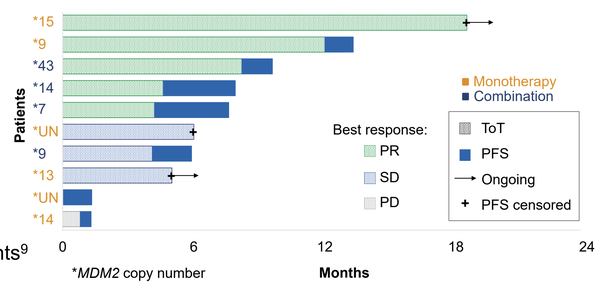
Lung adenocarcinoma[5] **5%**

Trial rationale

- Advanced biliary tract carcinoma and pancreatic ductal adenocarcinoma are associated with a median survival of ~1 year in the advanced stages, and effective therapies are needed[6,7]
- In two ongoing Phase I studies (1403-0001, 1403-0002), treatment with BI 907828 ± ezabenlimab (an anti-PD-1 antibody) was associated with initial signs of activity in selected advanced/metastatic solid tumours[8,9]

Efficacy summary and swimmer plot of patients with BTC treated in two Phase Ia/b trials (1403-0001/1403-0002)[9]

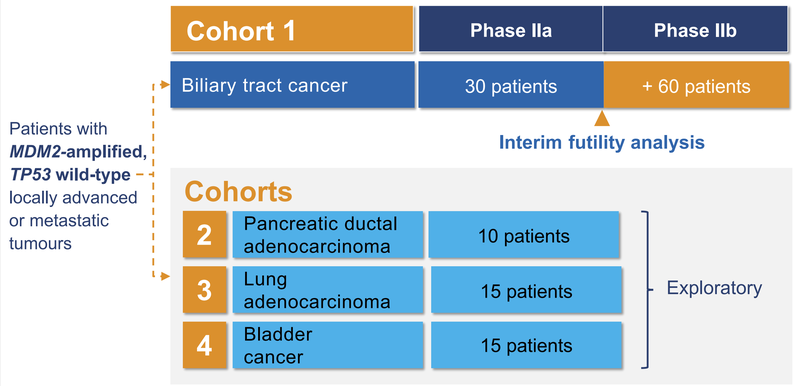
- In 10 patients with biliary tract carcinoma who received BI 907828 as monotherapy (n=6), or in combination with ezabenlimab (n=4), the objective response rate was 50% and three patients achieved stable disease as best response[9]
- Disease control lasting ≥6 months was observed in six out of 10 patients[9]



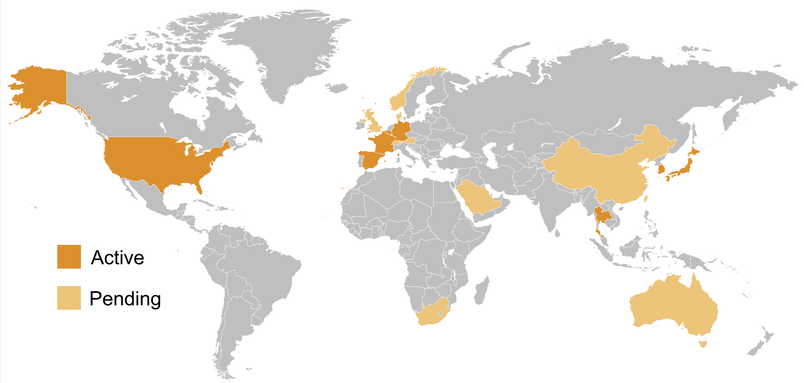
BTC, biliary tract cancer; MDM2, mouse double minute-2; p53, protein 53; PD-1, programmed cell death protein-1; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; SD, stable disease; ToT, time on treatment; *TP53*, tumour protein 53; UN, unknown; wt, wild-type

Trial design

Brightline-2 (NCT05512377): a multicentre, open-label, single-arm, Phase IIa/IIb trial, assessing the efficacy and safety of **BI 907828, an MDM2–p53 antagonist**



- BI 907828 45 mg monotherapy will be given orally on Day 1 of 3-week cycles. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent
- Patients must have advanced or unresectable *MDM2*-amplified, *TP53* wild-type solid tumours without treatment options
- Recruitment is into four cohorts according to tumour type. Active and pending sites are shown below. As of April 20th 2023, 22 patients with biliary tract carcinoma and two patients with pancreatic cancer have been enrolled across 12 sites in five countries



Objectives

Primary	Secondary	
• Evaluate efficacy of BI 907828: objective response rate	• Evaluate efficacy: duration of response, progression-free survival, overall survival	• Evaluate health-related quality of life: EORTC QLQ-C30, EORTC QLQ-BIL21 (Cohort 1) and others

Inclusion and exclusion criteria

Inclusion	Exclusion
Locally advanced or metastatic: • Biliary tract carcinoma • Pancreatic ductal adenocarcinoma • Lung adenocarcinoma • Bladder cancer	Previous administration of BI 907828 or any other MDM2–p53 or MDMX (MDM4)–p53 antagonist
Receipt of appropriate prior standard-of-care therapy	Major surgery performed ≤4 weeks prior to treatment on trial or planned ≤6 months after screening
Written report confirming *MDM2* amplification (copy number ≥8)	Previous or concomitant malignancies that may affect treatment efficacy or trial outcome
TP53 wild-type	Use of restricted medications or drugs likely to interfere with safe conduct of the trial
≥1 measurable lesion (RECIST v1.1)	Receiving treatment for brain metastases or leptomeningeal disease that may interfere with assessment of trial endpoints
ECOG performance status of 0/1	
Adequate organ function	

Endpoints

Primary	Secondary	
• Objective response rate by central independent review (RECIST v1.1)	• Duration of response and progression-free survival based on central independent review • Overall survival	• Disease control • Occurrence of adverse events and treatment-related adverse events while on-treatment

ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; QLQ, quality of life questionnaire; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

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